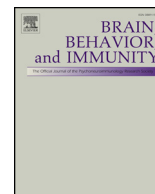




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Correlation between immune response and self-reported depression during convalescence from COVID-19



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ABSTRACT

Self-reported depression has been observed in coronavirus disease-2019 (COVID-19) patients, infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), during discharge from the hospital. However, the cause of this self-reported depression during the convalescent period remains unclear. Here, we report the mental health status of 96 convalescent COVID-19 patients who were surveyed using an online questionnaire at the Shenzhen Samii Medical Center from March 2 to March 12, 2020 in Shenzhen, China. After obtaining their informed consent, we retrospectively analyzed the clinical characteristics of patients, including routine blood and biochemical data. The results suggested that patients with self-reported depression exhibited increased immune response, as indicated by increased white blood cell and neutrophil counts, as well as neutrophil-to-lymphocyte ratio. However, the mechanism linking self-reported depression to these cellular changes needs further study. In conclusion, self-reported depression occurred at an early stage in convalescent COVID-19 patients, and changes in immune function were apparent during short-term follow-up of these patients after discharge. Appropriate psychological interventions are necessary, and changes in immune function should be emphasized during long-term follow up of these patients.

1. Introduction

The World Health Organization (WHO) has declared that the outbreak of coronavirus disease-19 (COVID-19), which is caused by infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a public health emergency of international concern. Since the outbreak of COVID-19 (Wang et al., 2020), more than 1.2 million people have been infected worldwide. People affected by this disease have been experiencing different degrees of anxiety, depression, panic attacks, and insomnia (Goulia et al., 2010; Tsang et al., 2004).

Apart from physical suffering, patients with confirmed or suspected COVID-19 have been reported to suffer from great psychological pressure and other health-related problems (Li et al., 2020). Moreover, confirmed and suspected cases of COVID-19 may experience fear of severe disease consequences and the contagion (Xiang et al., 2020). Consequently, they may experience loneliness, denial, anxiety,

depression, insomnia, and despair, which may lower treatment efficacy. A few of these patients may even be associated with increased risk of aggression and suicide attempts. Suspected isolated cases may suffer from anxiety due to uncertainty about their health status and develop obsessive-compulsive symptoms, such as repeated temperature check and sterilization. The degree of psychological stress in isolated patients has been found to be higher, and their psychological problems are prominent (Hawryluck et al., 2004). In addition, it was reported that healthcare workers in hospitals with lesser wards and workers for patients with COVID-19 in Wuhan and other regions of China experienced psychological burdens. Especially, nurses living in Wuhan and frontline healthcare workers who were directly involved in the diagnosis, treatment, and care of patients with COVID-19 were severely affected (Lai et al., 2020). An investigation of the mental health status of patients with novel coronavirus pneumonia revealed that the rates of depression, anxiety, sleep disorders, and physical symptoms were 49.06,

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56.60, 67.92, and 69.81%, respectively, and 24.53% of the patients were reported to engage in self-injury and suicide ideation (Zhao et al., 2020).

Innate and adaptive immune mechanisms provide effective defense against infections and regulate autoimmune responses. Infections can trigger chronic inflammation, which damages cognitive function. In humans, it has been observed that early hospitalization for patients with autoimmune disease or infectious disease can increase the risk of a major mood disorder by 45 and 62%, respectively (Pape et al., 2019). Depression is a widespread chronic illness that can affect thoughts, mood, and physical health. It is characterized by sadness, low mood, lack of energy, insomnia, and anhedonia (Novellino et al., 2020). Higher depression and anxiety scores are associated with an enhanced inflammatory state, as assessed by higher hematological inflammatory markers, including white blood cells (WBCs) and red blood cell distribution width (Shafiee et al., 2017). Observational studies have shown that other indicators of immunity, especially C-reactive protein (CRP) and proinflammatory cytokines, such as interleukin-6 (IL-6), are associated with an increased risk of depressive disorders (Haapakoski et al., 2016). In order to study the immune response and mental health status of convalescent COVID-19 patients, an online questionnaire and retrospective analysis of the physical examination data from these patients after discharge were completed. All patient information was collected with their informed consent.

2. Methods

2.1. Self-reported depression and epidemiological investigation in patients convalescing from COVID-19

All cured COVID-19 patients, according to the Guideline for the Diagnosis and Treatment of COVID-19 (the seventh trial edition) published by the National Health Commission of China, came from Shenzhen and were discharged from the Third People's Hospital of Shenzhen. With increased reports on the recurrence of positive SARS-CoV-2 RNA, all COVID-19 survivors in convalescence were under forced-quarantine and clinical observation for 14 days at the Shenzhen Samii Medical Center (SSMC) immediately after being discharged from the designated hospital since February 21, 2020 in Shenzhen, China. This study was conducted at SSMC, a municipal general hospital in Shenzhen, China. SSMC is the designated hospital for the isolation and observation of COVID-19 survivors during their early recovery stage, rendering it a suitable place to identify eligible study subjects. There were a total of 226 patients between February 21 to March 14, 2020 at SSMC. Among these, 126 patients completed the online questionnaire from March 2 to March 12, and 96 patients were clinically examined from March 5 to March 14, 2020. The online questionnaire was designed to investigate their mental health status in the isolation ward, including post-traumatic stress disorder (PTSD), post-traumatic stress disorder self-rating scale (PTSD-SS), Zung anxiety self-rating scale, and Zung self-rating depression scale (SDS). An SDS index score of 50 was the cut-off point for clinical significance (Zung, 1965). Epidemiological characteristics, including age, gender, comorbidities, potential effect of severity of initial infection, SARS-CoV-2 recurrence, and duration of initial illness (hospital stay, average number of days) were investigated in convalescent COVID-19 patients. Other COVID-19-related medical data were collected by telephone interviews and through checking medical records.

2.2. Analysis of the distribution characteristics of WBCs and inflammatory factors

Leukocytes can be used in individual patients to gauge the internal environment (Miyata et al., 2020), because they can be obtained at a clinically relevant time. We retrospectively analyzed the blood test data from cured COVID-19 patients. A total of 3 mL blood was extracted

from every patient, and the serum was separated by centrifugation at $2327 \times g$ for 15 min (L550; Hunan xiangyi laboratory instrument development co. LTD, China). Routine blood tests were performed using an automatic blood cell analyzer (XN1000; Sysmex, Japan). Detection principle: for WBCs, optical detection by semiconductor laser and flow cytometry was used. The reagents, controls, and calibrators used were original and operated according to the manufacturer's instructions. Routine blood tests included the total number of leukocytes and leukocyte count, including WBC count, neutrophil (NEUT) count, lymphocyte (LYM) count, monocyte count (MONO), eosinophil count (EOS), basophilic granulocyte count (BASO), neutrophil ratio (NEUT%), lymphocyte ratio (LYM%), monocyte ratio (MONO %), eosinophil ratio (EOS%), and basophilic granulocyte ratio (BASO%). The serum expression levels of the inflammatory factors, CRP and IL-6, were also analyzed. The serum was separated by centrifugation at $2327 \times g$ for 15 min. Serum biochemistry was performed using an automated biochemical analyzer (Cobas C501; Roche, Germany) for 30 min at 56°C for virus inactivation. IL-6 level was determined using an automatic chemiluminescence immunoassay system (Caris 200; WANTAI BioPharm, China). The reagents, controls, and calibrators used were original and operated according to the manufacturer's instructions.

2.3. Ethical statement

This study was approved by the Ethics Committee of Shenzhen Samii Medical Center (SSMC-R-20200401) and written informed consent was obtained from each patient.

2.4. Statistical analysis

All analyses were conducted with SPSS software version 19.0. Continuous variables were expressed as the means \pm standard deviation and a one-way analysis of variance (Tamhane's T2) was used to compare inter-group differences. Categorical variables were compared using Chi-square test. $p < 0.05$ was an indication of statistical significance.

3. Results

3.1. Epidemiological characteristics of cured COVID-19 patients with depression

According to the reference, patients with SDS index scores (index score = raw score \times 1.25) above 50 were considered to be prone to depression (Zung, 1965). The results indicated that 42 out of 96 cured COVID-19 patients had self-reported depressive symptoms during their convalescence.

To determine whether depression was related to epidemic background, we compared various data between the normal and self-reported depression groups. The results suggested that self-reported depression has no significant correlation with gender, age, comorbidity, severity of initial infection, and duration of initial illness. In addition, the viral nucleic acid test was positive for SARS-CoV-2 RNA in a few convalescent COVID-19 patients, and there was no statistical difference between two groups (Table 1).

3.2. Leukocyte distribution characteristics from cured COVID-19 patients with and without self-reported depression

WBCs are responsible for human immunity, especially when the body is infected by bacteria or viruses. The baseline WBC count in patients with depression has been reported to be $7.1 \times 10^9/\text{L}$ (Horsdal et al., 2017). After comparing the WBC counts between cured COVID-19 patients with and without self-reported depression, results showed that the WBC count was higher in the self-reported depression group ($6.7 \pm 1.5 \times 10^9/\text{L}$) than in the normal group ($6.0 \pm 1.5 \times 10^9/\text{L}$).

Table 1
Epidemiological characteristics of 96 discharged patients survived from COVID-19 infections in Shenzhen city and their psychological states.

Epidemiological characteristics		Normal (N = 54)	Self-reported Depression (N = 42)	F value	P value			
Potential effect of severity of initial infection (No., %)	Severe	8/54 (14.8)	5/42 (11.9)	0.171	0.679			
	Non-severe	46/54 (85.2)	37/42 (88.1)					
Hospital stay, average (days)		24.4 ± 6.7	24.8 ± 6.5	0.107	0.745			
Questionnaire times since from twice negative virus test (days)		6.2 ± 3.7	6.1 ± 3.9		0.864			
Age average (years)		45.2 ± 13.2	49.6 ± 13.2	2.576	0.112			
Age groups (No., %)	18–45	29/54 (53.7)	15/42 (35.7)	3.080	0.079			
	≥46	25/54 (46.3)	27/42 (64.3)					
Gender groups (No., %)	Female	27/54 (50.0)	22/42 (52.4)	0.054	0.817			
	Male	27/54 (50.0)	20/42 (47.6)					
Exposure to source within 14 days (No., %)	Wuhan exposure	17/54 (31.5)	17/42 (40.5)	0.836	0.361			
	No exposure	37/54 (68.5)	25/42 (59.5)					
Comorbidities (No., %)	At least one	22/54 (40.7)	16/42 (38.1)	0.069	0.793			
	No comorbidity	32/54 (59.3)	26/42 (61.9)					
	Hypertension	9/54 (16.7)	6/42 (14.3)			0.102	0.750	
	Diabetes	6/54 (11.1)	4/42 (9.5)			0.064	0.801	
	cardiovascular disease	4/54 (7.4)	2/42 (4.8)			0.282	0.595	
	Malignant tumor	1/54 (1.9)	1/42 (2.4)			0.032	0.857	
	Liver disease	5/54 (9.3)	2/42 (4.8)			0.707	0.400	
	Lung disease	1/54 (1.9)	0/42 (0)			0.786	0.375	
	Other disease	4/54 (7.4)	7/42 (16.7)			1.261	0.262	
	Positive of nucleic acid test after they dischargement (No., %)	Recurrence	3/54 (5.6)			4/42 (9.5)	0.550	0.458
		Non-recurrence	51/54 (94.4)			38/42 (90.5)		
	Hospital stay (No., %)	≤30 days	45/54 (83.3)			34/42 (81.0)	0.092	0.762
> 30 days		9/54 (16.7)	8/42 (19.5)					

Continuous variables were analyzed using one-way ANOVA (Tamhane's T2) test and the categorical variables were compared using Chi-square test (Monte Carlo Sig. T2).

Table 2
Comparison of immune factors in COVID-19 discharged patients.

Immune factors	Reference range	Normal group	Self-reported Depression	P value
WBC (10 ⁹ /L)	3.5–9.5	6.0 ± 1.5	6.7 ± 1.5* [†]	0.016
NEUT (10 ⁹ /L)	1.8–6.3	3.3 ± 0.9	4.1 ± 1.2*** [†]	0.000
LYM (10 ⁹ /L)	1.1–3.2	1.9 ± 0.6	1.8 ± 0.5	0.468
MON (10 ⁹ /L)	0.1–0.6	0.5 ± 0.2	0.5 ± 0.2	0.744
EOS (10 ⁹ /L)	0.02–0.52	0.1 ± 0.1	0.1 ± 0.1	0.568
BASO (10 ⁹ /L)	0–0.06	0.0 ± 0.0	0.0 ± 0.0	0.800
Neutrophil-to-Lymphocyte Ratio (NLR)	/	1.8 ± 0.6	2.4 ± 0.9*** [†]	0.000
NEUT ratio (%)	40–75	55.7 ± 6.4	61.0 ± 7.1*** [†]	0.000
LYM ratio (%)	20–50	32.3 ± 6.3	28.1 ± 6.7*** [↓]	0.002
BASO ratio (%)	0–1	0.7 ± 0.3	0.6 ± 0.3	0.107
EOS ratio (%)	0.4–8.0	2.2 ± 1.5	2.1 ± 1.4	0.741
MONO ratio (%)	3–10	9.0 ± 2.4	8.2 ± 2.6	0.148
HS-CRP (mg/dL)	0–0.5	0.1 ± 0.1	0.2 ± 0.3* [†]	0.035
IL-6 (pg/mL)	1.5–5000	56.1 ± 105.3	40.7 ± 65.6	0.518

Continuous variables were analyzed using one-way ANOVA (Tamhane's T2) test. *P < 0.05, **P < 0.01, ***P < 0.001 vs normal group. The symbols ↓ and † represented significantly higher or lower.

The NEUT count was significantly higher in the self-reported depression group (4.1 ± 1.2 × 10⁹/L) compared with the normal group (3.3 ± 0.9 × 10⁹/L) (p < 0.001; Table 2). Meanwhile, the neutrophil-to-lymphocyte ratio (NLR) was significantly higher in the self-reported depression group compared with the normal group (1.8 ± 0.6 in normal group vs 2.4 ± 0.9 in the depression group; p < 0.001).

Next, we detected the expression levels of important inflammatory immune factors, including CRP and IL-6. Baseline median CRP levels in patients with depression have been reported to be 2.8 mg/L (Horsdal et al., 2017). Here, the level of CRP was significantly higher in the self-reported depression group compared with the normal group (0.2 ± 0.3 vs 0.1 ± 0.1 mg/dL; p < 0.05). However, IL-6 levels were not significantly different between the two groups. These results suggested that self-reported depression might be closely associated with the immune status of the body.

4. Discussion

SDS is a self-rating instrument designed to detect symptoms related to depression and to measure the severity of depression in the general medical outpatient population (Zung, 1965). SDS consists of 20 items with a Likert-type scale, with raw scores that range from 20 to 80, which are converted to index scores by dividing the sum of the raw scores by 80, and then multiplying by 100. A raw score-index score conversion table has previously been provided by Zung (Zung, 1971). An SDS index score of 50 (raw score = 40) suggests clinically significant symptoms with the following three levels of severity ratings: index scores 25–49 (raw scores 20–40): normal; 50–59 (raw scores 41–47): mild to moderate; 60–69 (raw scores 48–55): moderate to severe; and 70 and above (raw scores 56 and above): severe (Zung, 1973). While SDS scales continue to be widely utilized, its application is associated with several challenges, with clinical cut-offs frequently being incorrectly applied (Dunstan and Scott, 2018). An SDS raw score of 50 has been recommended as the cut-off point for clinical significance (Dunstan and Scott, 2019). In order to help eliminate anxiety and mild depression in convalescent COVID-19 patients, we adopted a lower standard (index scores of 50) in this study. In patients with self-reported depression, even a small reduction of such risk may translate into better prognosis and improve quality of life.

Patients that have been cured from COVID-19 generally remain anxious and depressed, even after they are discharged from the hospital. The current study presented data on the short-term mental health consequences of COVID-19, which included chest tightness, insomnia, anorexia, and other symptoms. This might be caused due to infection with SARS-CoV-2 and the relatively long isolation period, which prevents patients from immediately returning home to their family. To obtain more adequate clinical data, a 1-year follow-up study will be conducted to monitor the mental health status of COVID-patients.

Depression is associated with immune system suppression, which may impair recovery. A previous study reported that the immune system was dramatically affected in patients after infection with SARS-CoV-2, leading to inflammation (Tay et al., 2020). Pulmonary recruitment of immune cells from the blood and infiltration of lymphocytes into the airways might cause lymphopenia, which increases the NLR in

around 80% of patients with infected with SARS-CoV-2 (Guan et al., 2020). There is a lack of data to verify whether these immune responses return to normal in COVID-19 patients after hospital discharge. Psychological stress has been shown to affect the immune system (Ménard et al., 2016). However, the relationship between SARS-CoV-2 infection-induced immune response and mental disorders remains unknown.

Increased numbers of WBCs and NEUTs provide insights into the various immune responses observed in cases of depression. The results from patients with self-reported depression demonstrated an increase in WBC and NEUT counts as well as NLR, which are similar to previous data on NLR and platelet-lymphocyte ratio in patients with different levels of depressive symptoms (Kayhan et al., 2017). NLR is calculated as ratio between absolute NEUT count and absolute LYM count. In a previous study, it was reported that NLR is increased in elderly patients after the first episode of depression (Arabska et al., 2018). Additionally, the NLR was significantly higher in unmedicated patients with depression than in healthy controls (2.10 ± 2.13 vs 2.01 ± 0.75 , $p = 0.004$), and it was higher after the first episode of depression than after recurrent episodes (2.11 ± 1.76 vs 1.64 ± 1.04 , $p < 0.05$). In our study, the NLR was significantly higher in the self-reported depression group compared with the normal group (2.4 ± 0.9 vs 1.8 ± 0.6 , $p < 0.001$). This indicates that NLR may serve as a clinical index for the diagnosis of self-reported depression at an early stage.

Based on the inflammatory factor profile in patients with depression, CRP and IL-6 are the most important regulated factors (Dowlati et al., 2010). It has been shown that elevation in CRP levels can increase the risk of depression (Valkanova et al., 2013). According to our analyses, the difference in CRP levels between the normal and self-reported depression groups was significant. However, the levels of IL-6, a specific biomarker of coronavirus infection, were not obviously different between the two groups. This may be because, after receiving treatment at the hospital, the levels of inflammatory factors in COVID-19 patients in the early recovery period are significantly reduced. Additionally, the potential effects of time delay between the blood test and completion of questionnaire should be considered.

For cured COVID-19 patients with self-reported depression, the mechanism of immune cell alteration remains unclear. Future studies should focus on the innate immune response of patients with self-depression, and the following factors should be investigated: 1) levels of T lymphocyte subsets, particularly $CD4^+$ and $CD8^+$ counts, and $CD4^+/CD8^+$ ratio, and NK cell count, and 2) the expression levels of serum neurotransmitters, including dopamine, 5-hydroxytryptamine (Maes et al., 1997), and norepinephrine.

In conclusion, self-reported depression may occur at an early stage in patients convalescing from COVID-19. Hence, after discharge, changes in immune function should be analyzed during long-term follow-up of these patients and appropriate psychological interventions should be undertaken.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

Bo Yuan, Wei Xin Li, and Cheng Wang conceived and designed the experiments. Hanqing Liu and Xin Cai analyzed the data. Shuo Song, Jia Zhao, Xiaopeng Hu, and Zhiwen Li collated the data. Kai Zhang, Zhi

yong Liu, and Jing Peng collected and tested the biological samples. Yongxin Chen, Bo Yuan, and Jianchun Wang obtained informed consent from the patients. Yawen An drafted and edited the manuscript. All authors reviewed the final manuscript and approved the submission.

Availability of data and materials

The datasets used in the current study are available from the corresponding author upon request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bbi.2020.05.062>.

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